17. (four times amended) The method of claim 14 [further comprising inserting human antibody amino acid sequence into the antibody in the constant domain or framework regions of the variable domain] wherein the antibody is humanized.

D4

Remarks

Telephone Call to Examiner's Superviser

A telephone call was made to the examiner's supervisor on February 6, 1998, requesting that the office action be reviewed and reissued. The supervisor stated that the office action would be reviewed and called the undersigned back, indicating that the rejection relating to the deposit with the ATCC appeared to be incorrect and should be withdrawn. The examiner is respectfully requested to consult with the supervisor in this regard since no interview summary has been received in the case.

Rejections under 35 U.S.C. §112

The specification was objected to and claims 1-3, 5, 7, 8, 14, 15, and 17-21 were rejected under 35 U.S.C. §112, first paragraph.

ATCC No. HB 9892

The antibody referred to in the claims and in the specification (HPC4) as deposited with the ATCC as ATCC NO. HB9892 is the subject of U.S. Patent Nos. 5,336,610 and 5,202,253, referenced at page 3, lines 13-15, to which this application claims priority. *A priori*, the enablement and deposit requirement for this antibody must have been met for these patents to issue since the claims are themselves drawn to the antibody and deposited

hybridoma secreting the antibody. Declarations regarding the availability of the deposited hybridoma and antibody expressed thereby were filed in these applications and are therefore public documents of the agreement by the depositor to maintain and make available the antibodies under the terms of the Budapest Treaty. As such, the patents are clear and convincing evidence of the public knowledge and availability of the deposited antibody. See 1158 OG 132, col. 2. There is no further requirement that applicants prove the antibody will be available forever, the requirement being "currently available". Id.; see also In re Metcalfe, 410 F.2d 1378, 161 USPQ 789 (CCPA 1969).

Rejections under 35 U.S.C. §102 or §103

Claims 1, 2, 5, 7, 8, and 20 were rejected under 35 U.S.C. §102(b) and (e) over U.S. Patent No. 5,202,253 or 5,147,638 to Esmon, et al. Claims 1, 2, 5, 7, 8, and 20 were rejected under §102(b) as disclosed by D'Angelo, et al., J. Clin. Invest. 77, 416-425 (1986) or Stearns, et al., J. Biol. Chem. 263(2) 826-832 (1988). Claims 1-3, 5, 7, 8, 14, 15, and 17-21 were rejected under §103 as obvious over U.S. Patent No. 5,202,253 or 5,147,638 to Esmon, et al., D'Angleo, et al., or Stearns, et al., in view of Morrison, Science 229, 1201-1207 (1985) or WO90/07861 by Protein Design Labs, Inc. ("Queen"). The claims were also rejected under the doctrine of obviousness-type double patenting over the same references. These rejections are respectfully traversed.

The claimed antibodies are novel

The examiner's point that merely stating that the antibodies contain "human amino acids" could be read as not distinguishing murine antibodies. Accordingly, the claims have been amended to recite that the antibodies are "humanized", as described in the specification beginning at page 15, line 25, expressed in recombinant expression systems such as bacteria or insect cells (all of which either cause the antibodies not to be glycosylated or which yield a different glycosylation than expression in mammalian cells) (support for the latter is provided explicitly at page 15, lines 5-14).

This should overcome any rejection under 35 U.S.C. §102.

The Claimed Antibodies are Distinct and not Predictable from the Prior Art

U.S. Patent Nos. 5,202,253 and 5,147,638

Neither U.S. Patent No. 5,202,253 nor 5,147,638 disclose nor claim a recombinant antibody; the patent is drawn to a naturally occurring **murine** antibody. The '253 reference does not enable a recombinant antibody, and certainly provides no guidance for how the antibody could be humanized.

Stearns

Stearns was cited as prior art to, and overcome during the prosecution of, the claimed murine monoclonal antibodies in the '638 and '253 patents. Stearns reported on the properties of the claimed murine monoclonal antibody but was determined not to enable one to make and use the antibody due to the unique characteristics of the antibody. If the article

could not enable and make obvious the antibody it described, it certainly could not enable and make obvious cloning and expression of a recombinant antibody sharing only the portion of the antibody conferring the unique specificity as claimed. No amino acid or nucleotide sequence is provided, nor would it be obvious from the protein.

D'Angelo

D'Angelo is an even less illuminating description of the murine monoclonal antibody referred to as HPC4, than the Stearns paper. Again, there is nothing that would enable the HPC4 antibody, much less cloning and manipulation so that the antibody could be expressed in either bacterial cells or incorporating human amino acid sequences.

Morrison and Queen

Morrison or Queen do not make up for these deficiencies. Neither provides the enablement to clone HPC4, nor provides any basis for believing that such a unique antibody could be cloned and still behave in its usual calcium dependent manner. It is clear that under §103 the art must not only motivate one to modify that which is disclosed in the prior art as applicants have done, but that there must be a reasonable expectation of success in doing so. The Examiner can point to no such support.

Summary

An antibody secreted by a murine hybridoma from murine antibody genes is not the same as the claimed antibody, which is either expressed in bacterial or insect cells or has been humanized.

As evidenced by the prosecution history in the '253 case, numerous experts submitted declarations under oath that even with undue experimentation they were unable to make by standard techniques monoclonal antibodies having the unique specificity of HPC-4: binding with one part of the antibody a peptide epitope and binding with another part of the antibody calcium. Until one had actually cloned the nucleotide sequence encoding HPC-4 and expressed it, it was not possible to predict that the isolated nucleotide sequence encoded HPC-4, much less whether it would be expressed in functional form. Recombinant fragments have been expressed in bacteria and shown to have the requisite binding activity. Humanized antibodies having the same specificity have now been made using standard techniques, based on the disclosed nucleotide sequence, by Genentech. In the absence of the nucleotide sequence, one cannot modify and genetically engineer the antibody to include non-murine amino acid sequence.

The Examiner's position is that the nucleotide sequence is obvious from the prior disclosure of the protein, i.e., the HPC-4 antibody. In the absence of the nucleotide sequence, one could not make the claimed antibody. It remains the position of the undersigned that the Court of Appeals in In re Deuel, 34 USPQ2d 1210 (Fed. Cir. 1995) that merely having the protein, or even some amino acid sequence (which is not described in the claims of the issued patent) would not be sufficient. The examiner has cited no art that discloses or makes obvious the amino acid sequence encoded by the recited nucleic acid. The art which has been cited by the Examiner discloses general methods to make chimeric

antibodies. This would not provide one skilled in the art with the methodology and a reasonable expectation of success that one could clone the hypervariable region of the HPC4 antibody, insert the cloned genes into an expression vector, and express antibody or antibody fragments having the requisite binding affinity. Even though the claimed subject matter is an antibody, the antibody **cannot be made except by expression of the nucleotide sequence**; accordingly, the antibody cannot be obvious from the naturally occuring antibody.

There are two basis on which the claimed antibodies are not obvious:

(1) the nucleotide sequence encoding the antibody was not known and the protein sequence of the antibody was not known, and

(2) the specificity of the antibody required the presence of two distinct molecules: calcium and a peptide epitope, a highly unusual situation for antibodies.

Applicants had attempted to make antibody fragments which had the requisite binding activity and found that the cleavage reactions generated many products, with loss of most activity. The definition of the hypervariable region, which was determined by cloning, was critical to construction and expression of defined portions of HPC4 and to humanization of the antibody. One skilled in the art simply could not have any basis for determining whether or not an antibody with the unique specificity of the HPC4 antibody could be cloned and this specificity expressed in a recombinant molecule. The Examiner has cited no evidence that one skilled in the art had ever attempted to clone such an antibody, much less had any success. The key to sustaining an obviousness rejection in this kind of situation is **not**

whether it was obvious to try, but **whether one skilled in the art would have an expectation of success**. HPC4 was a highly unusual antibody. As demonstrated by the declarations submitted in the prosecution of the patents claiming HPC4, unlike most monoclonals, HPC4 was impossible to duplicate. Calcium dependent antibodies immunoreactive to protein C, obtained by other parties, simply did not share the unique reactivity where calcium is essential to binding - merely having calcium present to alter binding **affinity** was not enough. This unique reactivity was obtained in the cloned, recombinant antibody - but this success, not well understood even after cloning, could not have been predicted.

The same general analysis as under §103 is applied under the doctrine of obviousness-type double patenting, but with regard solely to the issue of whether the claims in this application are obvious over the claims in the issued patent. For the same reasons that the claims are not obvious in view of the disclosures of these patents, they are even less obvious from the claims. The claimed murine antibody, and methods of use thereof, do not make obvious the nucleotide sequence required to make the recombinant antibody, nor is it predictable that even if one did clone the antibody, that the unique binding characteristics of HPC-4 would be transferred to the recombinant antibody.

Allowance of all claims 1, 3-5, 7, 8, 14, 15, and 17-2119 as amended, is earnestly solicited. All claims as pending upon entry of this amendment are attached in an appendix for the convenience of the examiner.

Respectfully submitted,

Patrea L. Pabst
Reg. No. 31,284

Date: June 3, 1998
ARNALL GOLDEN & GREGORY LLP
2800 One Atlantic Center
1201 West Peachtree Street
Atlanta, Georgia 30309-3450
(404) 873-8794

Certificate of Mailing under 37 CFR § 1.8(a)

I hereby certify that this Amendment is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the Assistant Commissioner of Patents, Washington, D.C. 20231.

Patrea L. Pabst

Date: June 3, 1998

APPENDIX: Claims as pending upon entry of this amendment

1. (four times amended) A recombinant Ca^{2+} dependent monoclonal antibody or antibody fragment including a heavy chain and a light chain, wherein the antibody or antibody fragment comprise the hypervariable regions of the monoclonal antibody produced by the hybridoma deposited with the American Type Culture Collection as ATCC No. HB 9892 which bind an epitope in the activation peptide region of the heavy chain of Protein C defined by E D Q V D P R L I D G K (Sequence ID No. 1) and calcium ions, where the antibody and antibody fragment inhibit Protein C activation by thrombin-thrombomodulin, and wherein the antibody and antibody fragment are expressed in bacterial or insect cells or [contains human amino acid sequence] is humanized.

2. (amended) The antibody of claim 1 comprising an amino acid sequence selected from the group consisting of:
MGRLSSSFLL LIAPAYVLSQ VTLKESGPGI LQPSQTLTLT CSLSGFSLRT SGMGVGWIRQ PSGKGLEWLA HIWWDDDKRY NPVLKSRLII SKDTSRKQVF LKIASVDTAD TATYYCVRMM DDYDAMDYWG QGTSVTVSS (Sequence ID No. 10); MDFQVQIFSF LLISASVIMS RGQIILTQSP AIMSASLGEE ITLTCSATSS VTYVHWYQQK SGTSPKLLIY GTSNLASGVP SRFSGSGSGT FYSLTVSSVE AEDAADYYCH QWNSYPHTFG GGTKLEIKR (Sequence ID No. 12); Q VTLKESGPGI LQPSQTLTLT CSLSGFSLRT SGMGVGWIRQ PSGKGLEWLA HIWWDDDKRY NPVLKSRLII SKDTSRKQVF LKIASVDTAD TATYYCVRMM DDYDAMDYWG QGTSVTVSS (amino acids 20-139 of Sequence ID No. 10) and QIILTQSP AIMSASLGEE ITLTCSATSS VTYVHWYQQK SGTSPKLLIY GTSNLASGVP SRFSGSGSGT FYSLTVSSVE AEDAADYYCH QWNSYPHTFG GGTKLEIKR (amino acids 23-129 of Sequence ID No. 12).

3. (three times amended) The antibody of claim 1 humanized by the inclusion of a [comprising] human [amino acid sequence in the] constant domain or framework regions of the variable domain.

5. (amended) A composition comprising the antibody of claim 1 in combination with a pharmaceutically acceptable carrier for administration to a patient.

7. (amended) The antibody of claim 1 having a detectable label directly bound to the antibody.

8. (twice amended) The antibody of claim 1 immobilized to a substrate which does not interfer with binding of the antibody to protein C in combination with calcium ions, wherein the immobilized antibody is suitable for purification of protein C from a biological fluid.

14. (four times amended) A method of making a recombinant Ca^{2+} dependent monoclonal antibody which binds an epitope in the activation peptide region of the heavy chain of Protein C defined by E D Q V D P R L I D G K (Sequence ID No. 1) and calcium ions, where the antibody inhibits Protein C activation by thrombin-thrombomodulin, by

expressing nucleotide molecules encoding the hypervariable region of the heavy and light chains of the monoclonal antibody expressed by the hybridoma deposited with the American Type Culture Collection as ATCC No. HB 9892 in bacteria or insect cells.

15. (amended) The method of claim 14 wherein the antibody comprises an amino acid sequence selected from the group consisting of:
MGRLSSSFLL LIAPAYVLSQ VTLKESGPGI LQPSQTLTLT CSLSGFSLRT SGMGVGWIRQ PSGKGLEWLA HIWWDDDKRY NPVLKSRLII SKDTSRKQVF LKIASVDTAD TATYYCVRMM DDYDAMDYWG QGTSVTVSS (Sequence ID No. 10); MDFQVQIFSF LLISASVIMS RGQIILTQSP AIMSASLGEE ITLTCSATSS VTYVHWYQQK SGTSPKLLIY GTSNLASGVP SRFSGSGSGT FYSLTVSSVE AEDAADYYCH QWNSYPHTFG GGTKLEIKR (Sequence ID No. 12); Q VTLKESGPGI LQPSQTLTLT CSLSGFSLRT SGMGVGWIRQ PSGKGLEWLA HIWWDDDKRY NPVLKSRLII SKDTSRKQVF LKIASVDTAD TATYYCVRMM DDYDAMDYWG QGTSVTVSS (amino acids 20-139 of Sequence ID No. 10) and QIILTQSP AIMSASLGEE ITLTCSATSS VTYVHWYQQK SGTSPKLLIY GTSNLASGVP SRFSGSGSGT FYSLTVSSVE AEDAADYYCH QWNSYPHTFG GGTKLEIKR (amino acids 23-129 of Sequence ID No. 12).

17. (four times amended) The method of claim 14 [further comprising inserting human antibody amino acid sequence into the antibody in the constant domain or framework regions of the variable domain] wherein the antibody is humanized.

18. (amended) The method of claim 14 further comprising directly binding detectable label to the antibody.

19. (amended) The method of claim 14 further comprising immobilizing the antibody to a substrate which does not interfer with binding of the antibody to protein C in combination with calcium ions, wherein the immobilized antibody is suitable for purification of protein C from a biological fluid.

20. (amended) The recombinant antibody of claim 1 having coupled thereto a peptide sequence.

21. (amended) The method of claim 14 wherein the nucleotide sequence encoding the recombinant antibody is ligated to a sequence encoding a peptide and the ligated nucleotide sequence is expressed in an expression system.